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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,490	04/06/2001	Elizabeth S. Stuart	08952-008001 / UMA 00-19	5744
26161	7590	04/19/2005	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			FORD, VANESSA L.	
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			1645	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/827,490	<b>Applicant(s)</b> STUART ET AL.	
	<b>Examiner</b> Vanessa L. Ford	<b>Art Unit</b> 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 7,9,10 and 18-20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7,9,10 and 18-20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

**FINAL ACTION**

1. This Office Action is responsive to Applicant's amendment and response filed January 14, 2005. Claims 7 and 18 have been amended. Claim 20 has been added. Claims 1-6, 8 and 11-17 have been cancelled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

***Rejections Withdrawn***

3. The following rejections are withdrawn in view of Applicant's amendment.

a) rejection of claim 15 under 35 U.S.C. 102(b), pages 3-6, paragraph 4 of the previous Office action.

b) rejection of claim 18 under 35 U.S.C.103(a), pages 12, paragraph 8 of the previous Office action.

***Rejections Maintained***

4. The rejection under 35 U.S.C. 103(a) is maintained for claims 7, 9, 18-19 and newly submitted claim 20 for the reasons set forth on pages 6-9, paragraph 5 of the previous Office Action.

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The rejection was on the grounds Whittum-Hudson et al teach that the chlamydial exoglycolipid antigen (GLXA) is expressed at all differentiation stages of the *Chlamydia* organisms and is secreted from infected cells (page 1116, 2<sup>nd</sup> column). Whittum-Hudson et al teach that GLXA is a unique chlamydial antigen. Whittum-Hudson et al teach that the antigenic determinants of GLXA resides on its polysaccharide component thus making it a T-independent antigen, as such GLXA will not be expected to generate protective IgG antibody responses or T-helper cell responses (page 1116, 2<sup>nd</sup> column). Whittum-Hudson et al teach GLXA is specific for the 89MS30 antibody therefore, GLXA is capable of binding the 89MS30 antibody (page 1117, 2<sup>nd</sup> col). Whittum-Hudson et al teach that anti-idiotypic antibodies have been suggested as alternatives to purified antigens as vaccine candidates particularly when antigen preparation is technically difficult as for tumor-specific antigens or bacterial carbohydrate antigens (page 1117, 1<sup>st</sup> column). Whittum-Hudson et al teach that anti-ID to GLXA represents both functional and molecular mimicry of GLXA, it induces anti-GLXA responses and according to competitive inhibition studies mimics the combining sites of monoclonal antibody mAb<sub>1</sub> and antibody Ab<sub>3</sub> for GLXA (page 1117, 1<sup>st</sup> column). However, Whittum-Hudson et al also teach that the use of anti-Id for infectious agents has been limited in part because of the difficulty in delivery of antibodies to the mucosal immune system, particularly as fed vaccines (page 1117, 1<sup>st</sup> column).

Whittum-Hudson et al teach do not teach a carrier group covalently coupled to the GLXA.

Dick, Jr. et al teach that conjugation of bacterial carbohydrate antigens to a carrier protein. Dick, Jr. et al teach that some subjects (e.g. children under 18 months and elderly people) fail to produce antibodies when stimulated with capsular polysaccharide immunogens (CPS) at level too low to be protective (page 49). Dick, Jr. et al teach that high-risk populations retain the ability to produce protective antibodies against immunogenic proteins such as diphtheria toxoid or tetanus toxoid by a process that can be adapted to carbohydrate antigens (page 49). Dick, Jr. et al teach that proteins and polysaccharides are classified into two separate classes of antigens thymus dependent (TD) and thymus independent (TI) antigens, respectively (page 49). Dick et al teach that polysaccharides classified as TI antigens have multiple repeat epitopes on their polymeric chains which collectively bind and cross-link immunoglobulin receptors on the surface of B cells and the net effect is the induction of cellular differentiation processes that yield antibody-producing plasma cells (page 49). Dick, Jr. et al teach that it is well established that covalent bonding of carbohydrate antigens demonstrate a thymus dependent (TD) response to carbohydrate components (page 49 and 58). Dick, Jr. et al teach that CPS can be linked to carrier proteins directly or by bifunctional linkers (spacer arms) (pages 71-72) which overcome conjugation limitations imposed by steric effects (page 71). Dick, Jr. et al teach that linkers can promote improved antigenicity for the bound components as compared to results obtained when testing the same antigens conjugated by a direct method (page 72). Dick, Jr. et al teach that spacers (i.e. linkers) permit corresponding increases in translational and rotational characteristics of the antigens, increasing access of the binding sites to soluble antigens

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(page 72). Dick, Jr. et al teach that linkers can be covalently bound to carbohydrate components (page 70).

It would be *prima facie* obvious at the time the invention was made to use covalently couple the oligosaccharide/polysaccharide of chlamydial GLXA as taught by Whittum-Hudson et al to a carrier protein (e.g. diphtheria toxoid or tetanus toxoid) as taught by Dick, Jr. et al because Whittum-Hudson et al teach that GLXA is abundant in *Chlamydia* species as well as being antigenic and Dick, Jr. et al teach that carbohydrate components can be covalently linked to carrier proteins thereby, demonstrating a thymus dependent (TD) response to carbohydrate components and enhancing the immune response to carbohydrate component. It would be expected barring evidence to the contrary, a composition comprising GLXA covalently coupled to a carrier protein would be effective in stimulating a response from the immune system since the polysaccharide component has been demonstrated to be antigenic. One of skill in the art would have been motivated to produce the immunogen as combined because Whittum-Hudson et al teach that the use of anti-Id for infectious agents has been limited in part because of the difficulty in delivery of antibodies to the mucosal immune system, particularly as fed vaccines.

Applicant urges that the claims are not rendered obvious over the combination of prior art references. Applicant urges that Whittum-Hudson et al do not describe, or even suggest an isolated GLXA oligosaccharide covalently coupled to a carrier group.

Applicant urges that nowhere does Whittum-Hudson et al disclose or suggest that useful oligosaccharide should or could be isolated from GLXA and coupled to a carrier.

Applicant urges that Dick, Jr. et al do not provide the information missing from Whittum-Hudson et al. Applicant urges that Dick, Jr. et al disclose how to make certain

glycoconjugate vaccines but does not describe GLXA. Applicant urges that a skilled

practitioner would not be motivated by Dick Jr. et al to modify the methods described in

Whittum-Hudson et al to create the compositions recited in the claims. Applicant urges

that Whittum-Hudson et al teach away from making such compositions. Applicant urges

that Whittum-Hudson et al suggest using anti-idiotypic antibodies to make a vaccine

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against chlamydial infection. Applicant urges that Whittum-Hudson et al demonstrate that when mice were immunized with either a soluble anti-idiotypic antibody (mAb<sub>2</sub>) or with GLXA only mAb<sub>2</sub> was protective against subsequent chlamydial challenge.

Applicant urges that given that GLXA was not protective no practitioner would be motivated to isolate an oligosaccharide from GLXA and couple it to a carrier group.

Applicant urges that neither of the cited references, alone or in combination provide a teaching or a motivation for a skilled artisan to arrive at the claimed invention. Applicant urges that the Office has failed to make a case of *prima facie* obviousness.

Applicant's arguments filed January 14, 2005 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The Examiner disagrees with Applicant assertion the "the cited art does not teach a GLXA oligosaccharide". It should be noted that Whittum-Hudson et al disclose the generation of the same GLXA oligosaccharide as that disclosed in the instant application (see page 4063 of the prior art and pages 14-15 of the instant specification). It should be noted that Whittum-Hudson et al teach that GLXA has an immunogenic epitope that is a carbohydrate which does not have lasting immunogenic memory (page 4062). Whittum-Hudson et al also teach that GLXA is recognized by serum antibodies from patients and animals infected by at least three species of *Chlamydia* and therefore, demonstrates genus-specificity (page 4062). One of ordinary skill in the art would be motivated to couple an GLXA oligosaccharide to

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a carrier because Dick, Jr. et al teach that carbohydrate components can be covalently linked to carrier proteins thereby, demonstrating a thymus dependent (TD) response to carbohydrate components and enhancing the immune response to carbohydrate component. Additionally, Whittum-Hudson et al teach that it has been demonstrated that protection T cells are required for long-lasting protection (page 4068). It would be expected that a composition comprising GLXA covalently coupled to a carrier protein would be effective in stimulating a response from the immune system since the carbohydrate component has been demonstrated to be immunogenic and genus-specific. Therefore, a person of ordinary skill in the art would not conclude that the combination of references teach away from making a GLXA oligosaccharide coupled to a carrier protein. In fact, the combination of references support the production of these conjugates. Whittum-Hudson et al teach that the oligosaccharide binds to anti-chlamydial glycolipid exoantigen monoclonal antibody 89MS30 because 89MS30 is a monoclonal antibody (mAb1) which is raised against GLXA (page 4062 and page 15 of the instant specification).

In response to applicant's argument that there is no *prima facie* case of obviousness established by the Office, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed.

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Cir. 1992). There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

5. The rejection under 35 U.S.C. 103(a) is maintained for claim 10 for the reasons set forth on pages 9-10, paragraph 6 of the previous Office Action.

The rejection was on the grounds that the teachings of Whittum-Hudson and Dick, Jr. et al have been described above.

The combination of Whittum-Hudson et al and Dick, Jr. et al as set forth *supra* does not teach that the linker is 2-(4-aminophenyl)ethylamine.

Semprevivo teaches 2-(4-aminophenyl)ethylamine linkers. Semprevivo teaches that oligosaccharides behave as simple haptens and must be linked either to proteins or a solid support in order to raise and isolate a specific antibody (see the Abstract). Semprevivo teaches that all oligosaccharides regardless of size become associated with the carrier protein (page 225). Semprevivo teaches that coupling oligosaccharides with a 2-(4-aminophenyl)ethylamine linker conserves that chemical integrity of the oligosaccharide.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the 2-(4-aminophenyl)ethylamine linkers as taught by Semprevivo to covalently bond the carrier group (diphtheria toxoid or tetanus toxoid) to the oligosaccharide of Whittum-Hudson et al and Dick, Jr. et al as combined above because Semprevivo has demonstrated that 2-(4-aminophenyl)ethylamine linkers can be used to form oligosaccharide-protein conjugates (see the Abstract). One would be motivated use of 2-(4-aminophenyl)ethylamine linkers to produce the claimed chlamydial glycolipid-oligosaccharide conjugated of because 2-(4-aminophenyl)ethylamine teach the 2-(4-aminophenyl)ethylamine can be used to couple proteins via their phenylisothiocyanate intermediates under conditions that preserve labile sugar linkages (see the Abstract). Additionally, Dick, Jr. et al teach that carbohydrate components can be covalently linked to carrier proteins to enhance the immune response to the response to carbohydrate component.

Applicant urges that Semprevivo does not cure the deficiencies of Whittum-Hudson et al and Dick, Jr. et al. Applicant urges that Semprevivo does not describe any chlamydial glycolipids much less isolated GLXA oligosaccharides. Applicant urges that Semprevivo does not disclose or suggest methods that could be utilized with glycolipids from prokaryotes of the genus *Chlamydia* or any prokaryotic organism. Applicant urges



that given Semprevivo's lack of instruction on these issues the skilled practitioner could not have reasonably expected to be successful in using Semprevivo's methods with GLXA oligosaccharides. Applicant urges that neither of the cited references, alone or in combination provide a teaching or a motivation for a skilled artisan to arrive at the claimed invention.

Applicant's arguments filed January 14, 2005 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. One of ordinary skill in the art would be motivated to use the 2-(4-aminophenyl)ethylamine linkers as taught by Semprevivo to covalently bond the carrier group (diphtheria toxoid or tetanus toxoid) to the oligosaccharide of as combined above because Semprevivo has demonstrated that 2-(4-aminophenyl)ethylamine linkers can be used to form oligosaccharide-protein conjugates (see the Abstract). One of ordinary skill in the art would be motivated use of 2-(4-aminophenyl)ethylamine linkers to produce the claimed chlamydial glycolipid-oligosaccharide conjugates because Semprevivo teaches that 2-(4-aminophenyl)ethylamine can be used to couple proteins *via* their phenylisothiocyanate intermediates under conditions that preserve labile sugar linkages (see the Abstract). Additionally, Dick, Jr. et al teach that carbohydrate components can be covalently linked to carrier proteins to enhance the immune response to the response to carbohydrate component and Dick, Jr. et al teach that carbohydrates can be linked to carrier proteins

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directly or by bifunctional linkers (spacer arms) (pages 71-72) which overcome conjugation limitations imposed by steric effects (page 71). Thus, one of ordinary skill in the art would expect success when using 2-(4-aminophenyl)ethylamine to conjugate GLXA and a carrier molecule. Therefore, the combination of references suggest that carbohydrate conjugates can be made via 2-(4-aminophenyl)ethylamine linkers. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

6. The rejection under 35 U.S.C. 103(a) is maintained for claim 10 for the reasons set forth on pages 11-12, paragraph 7 of the previous Office Action.

The rejection was on the grounds that the teachings Whittum-Hudson et al and Dick, Jr. et al have been described above.

The combination of Whittum-Hudson et al and Dick, Jr. et al as set forth *supra* does not teach that the linker is 2-(4-aminophenyl)ethylamine.

Smith et al teach the  $\beta$ -(p-aminophenyl)ethylamide (i.e. 2-(4-aminophenyl)ethylamine) can be used to couple proteins via their phenylisothiocyanate intermediates under conditions that preserve labile sugar linkages (see the Abstract). Smith et al teach the coupling of oligosaccharides to bovine serum albumin and keyhole limpet hemocyanin (see the Abstract). Smith et al teach that rabbits immunized with the synthetic glycoproteins produced antibodies directed against the oligosaccharides (see the Abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the  $\beta$ -(p-aminophenyl)ethylamide (i.e. 2-(4-aminophenyl)ethylamine) linkers as taught by Smith et al to covalently bond the carrier group (diphtheria toxoid or tetanus toxoid) to the oligosaccharide of Whittum-Hudson et al and Dick, Jr. et al as combined above because Smith et al have demonstrated that  $\beta$ -(p-aminophenyl)ethylamide linkers can be used to form oligosaccharide-protein conjugates (see the Abstract). One would be motivated use of  $\beta$ -(p-aminophenyl)ethylamine linkers to produce the claimed chlamydial glycolipid-oligosaccharide conjugated of because Smith et al teach the  $\beta$ -(p-aminophenyl)ethylamide (i.e. 2-(4-aminophenyl)ethylamine) can be used to couple proteins via their phenylisothiocyanate intermediates under conditions that preserve labile sugar linkages (see the Abstract). Additionally, Dick, Jr. et al teach that

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carbohydrate components can be covalently linked to carrier proteins to enhance the immune response to the response to carbohydrate component.

Applicant urges that Smith does not cure the deficiencies of Whittum-Hudson et al and Dick, Jr. et al. Applicant urges that Smith et al do not describe any chlamydial glycolipids much less isolated GLXA oligosaccharides. Applicant urges that Smith et al do not disclose or suggest methods that could be utilized with glycolipids from prokaryotes of the genus *Chlamydia* or any prokaryotic organism. Applicant urges that neither of the cited references, alone or in combination provide a teaching or a motivation for a skilled artisan to arrive at the claimed invention. Applicant urges that it appears that the Office is relies on the present application as a roadmap to show how to combine the references. Applicant urges that the prior art must suggest the combination of teachings and that such a combination would have a reasonable likelihood of success. Applicant urges that "obvious to try" is not the proper standard in an obviousness analysis.

Applicant's arguments filed January 14, 2005 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. One of ordinary skill in the art would be motivated to use the  $\beta$ -(p-aminophenyl)ethylamide (i.e. 2-(4-aminophenyl)ethylamine) linkers as taught by Smith et al to covalently bond the carrier group (diphtheria toxoid or tetanus toxoid) to the oligosaccharide as combined above because Smith et al have

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demonstrated that  $\beta$ -(p-aminophenyl)ethylamide linkers can be used to form oligosaccharide-protein conjugates (see the Abstract). One of ordinary skill in the art would be motivated <sup>to</sup> use  $\beta$ -(p-aminophenyl)ethylamine linkers to produce the claimed chlamydial glycolipid-oligosaccharide conjugates because Smith et al teach that the  $\beta$ -(p-aminophenyl)ethylamide can be used to couple proteins *via* their phenylisothiocyanate intermediates under conditions that preserve labile sugar linkages (see the Abstract). The Examiner disagrees with Applicant's assertion that combining the prior art references is "obvious to try". It should be noted the Dick, Jr. et al teach that carbohydrate components can be covalently linked to carrier proteins to enhance the immune response to the response to carbohydrate component and Dick, Jr. et al teach that carbohydrates can be linked to carrier proteins directly or by bifunctional linkers (spacer arms) (pages 71-72) which overcome conjugation limitations imposed by steric effects (page 71). Therefore, the combination of references suggest that carbohydrate conjugates can be made via the  $\beta$ -(p-aminophenyl)ethylamide linkers. Thus, one of ordinary skill in the art would expect success when using the  $\beta$ -(p-aminophenyl)ethylamide to conjugate GLXA and a carrier molecule.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

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reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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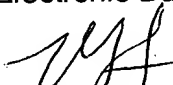
**Conclusion**

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Vanessa L. Ford  
Biotechnology Patent Examiner  
April 12, 2005

  
**LYNETTE R. F. SMITH**  
**SUPERVISORY PATENT EXAMINER**  
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